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Predicting the Long-Term Effects of Cardiac Resynchronization Therapy on Mortality From Baseline Variables and the Early Response

A Report From the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial

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Objectives This study was designed to investigate whether selected baseline variables and early response markers predict the effects of cardiac resynchronization therapy (CRT) on long-term mortality.

Background Cardiac resynchronization therapy reduces long-term morbidity and mortality in patients with moderate or severe heart failure and markers of cardiac dyssynchrony, but not all patients respond to a similar extent.

Methods In the CARE-HF (Cardiac Resynchronization in Heart Failure) study, 813 patients with heart failure and markers of cardiac dyssynchrony were randomly assigned to receive or not receive CRT in addition to pharmacological treatment and were followed for a median of 37.6 months. A model including assigned treatment, 15 pre-specified baseline variables, and 8 markers of response at 3 months was constructed to predict all-cause mortality.

Results On multivariable analysis, plasma concentration of amino terminal pro–brain natriuretic peptide (univariate and multivariable model chi-square test: 105.0 and 48.4; both $p < 0.0001$) and severity of mitral regurgitation (chi-square test: 44.0 and 17.9; both $p < 0.0001$) at 3 months, regardless of assigned treatment, were the strongest predictors of mortality. Ischemic heart disease as the cause of ventricular dysfunction (chi-square test: 34.9 and 7.4; $p < 0.0001$ and $p = 0.0066$), being in New York Heart Association functional class IV (chi-square test: 18.8 and 9.6; $p < 0.0001$ and $p = 0.0020$), or having *less* interventricular mechanical delay (chi-square test: 29.8 and 8.8; $p < 0.0001$ and $p = 0.0029$) at baseline all predicted a worse outcome. However, the reduction in mortality in patients assigned to CRT was similar before (hazard ratio: 0.602; 95% confidence interval: 0.468 to 0.774) and after (hazard ratio: 0.679; 95% confidence interval: 0.494 to 0.914) adjustment for variables measured at baseline and at 3 months.

Conclusions Patients who have more severe mitral regurgitation or persistently elevated amino terminal pro–brain natriuretic peptide despite treatment for heart failure, including CRT, have a higher mortality. However, patients assigned to CRT had a lower mortality even after adjusting for variables measured before and 3 months after intervention. The effect of CRT on mortality cannot be usefully predicted using such information. (CARE-HF CArdiac Resynchronization in Heart Failure; NCT00170300) (J Am Coll Cardiol 2008;52:438–45) © 2008 by the American College of Cardiology Foundation

In patients with moderate or severe heart failure due to left ventricular (LV) systolic dysfunction and QRS prolongation on the surface electrocardiogram, cardiac resynchronization therapy (CRT) improves heart function, symptoms, quality of life, and prognosis (1–4). The clinical response to CRT is variable, with a continuous spectrum ranging from dramatic to disappointing (5), and, so far, its prediction from baseline variables has met with limited success. A series of small observational trials has suggested that cardiac dyssynchrony measured by a variety of echocardiographic techniques might predict the response to CRT (5). For example, Penicka et al. (6) studied 49 patients and concluded that echocardiographic measures of both intra- and interventricular dyssynchrony predicted improvement in ventricular function at 6 months. In a study of 54 patients, Yu et al. (7)

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reported that tissue Doppler imaging predicted improvement in ventricular function at 6 months. Similarly, Bax et al. (8) studied 80 patients who received CRT using tissue Doppler imaging and reported that the risk of death or hospitalization with heart failure at 1 year was only 6% in the 49 patients with intraventricular dyssynchrony >65 ms but 50% in those with less marked dyssynchrony. This could reflect an intrinsically better prognosis in patients with dyssynchrony or a treatment effect. It is not clear whether the use of short-term improvements in ventricular function as a surrogate measure of long-term clinical response is appropriate, and the few attempts using data from randomized controlled trials have, so far, been unable to corroborate these findings, although the techniques used might now be considered outmoded (9). Recently, a large prospective, observational study (PROSPECT [Predictors of Response to CRT] trial) was unable to find clinically useful predictors of the response to CRT over 6 months in terms of clinical status or improvement in LV function (10).

The complex and varied reasons for failure to respond to CRT may be the reason that no robust pre-implantation marker of therapeutic response to CRT has yet been found. Patient factors may include the severity and type of dyssynchrony, the extent and location of myocardial scarring, and the severity of and reasons for mitral regurgitation (5,11). It is also likely that dyssynchrony may develop, and perhaps disappear, as ventricular dysfunction progresses. The success of CRT will also depend on the technical success of lead positioning and device programming. An alternative approach to try to assess the role of dyssynchrony in determining the long-term response to CRT is to investigate whether the initial response to therapy predicts long-term outcome, because this simultaneously tests both the patient substrate and the adequacy of implementation of CRT. For example, Yu et al. (12) noted that changes in ventricular function 3 to 6 months after implantation but not changes in symptoms predicted long-term survival in an observational study of 141 patients. Kubanek et al. (13) noted that change in natriuretic peptides at 3 months predicted clinical improvement at 1 year in a study of 43 patients. However, responses to concomitant pharmacological treatment, the existence of comorbid conditions, intercurrent events, and "placebo" effects will be important additional determinants of the apparent clinical response to CRT in observational trials.

An observational study can address the question of whether a patient who receives CRT will do well or not, but cannot tell whether the intervention changed the course of the disease because it lacks a control group. Randomized trials are required to prove whether an intervention alters the natural history of disease. A patient who dies 1 year after receiving CRT might be considered to have had an excellent response if similar patients in the control group die within a few weeks. Similarly, some patients who appear to respond very well to CRT might do just as well without it.

Clearly, CRT reduces long-term mortality. However, if the effects of CRT on mortality can be explained by either baseline measures of dyssynchrony and/or the initial response to therapy, then being randomized to CRT should no longer be associated with reduced mortality after adjustment for these factors. Accordingly, we undertook an analysis to identify whether baseline variables and the early response to CRT could explain its effects on long-term mortality in the CARE-HF (Cardiac Resynchronization in Heart Failure) trial.

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
ESVI = end-systolic volume index
IVMD = interventricular mechanical delay
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
NT-proBNP = amino terminal pro-brain natriuretic peptide

Methods

The CARE-HF trial was a multicenter, international, randomized trial that compared the effect of implanting or not implanting a CRT device in patients with moderate or severe symptoms of heart failure despite treatment with loop diuretics, a left ventricular ejection fraction (LVEF) <35%, and markers of cardiac dyssynchrony, in sinus rhythm and receiving standard pharmacologic therapy, generally including angiotensin-converting enzyme inhibitors, beta-blockers, and, for more severe cases, spironolactone. CRT-only devices *without* a defibrillator function were used. A QRS duration ≥120 ms was used as a marker of cardiac dyssynchrony, but patients with QRS durations of 120 to 149 ms required at least 2 additional echocardiographic markers of dyssynchrony: an aortic pre-ejection delay >140 ms, an interventricular mechanical delay >40 ms, or delayed activation of the posterolateral LV wall. Patients and investigators were not blinded to treatment allocation, because the control group did not receive a device. Further details of the design, inclusion criteria, baseline clinical and echocardiographic characteristics, and the main results have been published elsewhere (2,3,14).

The steering committee designed the trial. Medtronic Bakken Research Center funded the trial and helped to implement it. The sponsor had no access to the database and did not participate in the analysis. All statistical analyses were performed by 1 of the authors (N.F.).

The study was approved by the local ethics committee of each participating institution and by appropriate national ethics committees. All patients provided written informed consent.

Implant procedure and device programming. Multiple attempts at device implantation were permitted. Device implantation, predominantly of the InSync III Model 8042 (Medtronic, Maastricht, the Netherlands), was successful on the first attempt in 349 patients (85%), on the second in 34 (8%), and on the third in 7 (2%). Finally, 390 of 409

patients (95%) had a system implanted and activated. Left ventricular leads were from the Attain product line (Medtronic). Standard bipolar right atrial and ventricular leads were used. Investigators were requested to try to pace the lateral or posterolateral LV wall via a lateral coronary vein and to pace the right ventricle at the site with the longest delay from LV stimulation to right ventricular detection, which is usually near the apical septum. Echocardiography was used to identify the end of atrial systole from the mitral Doppler signal, which was considered the optimal atrioventricular delay. Interventricular delay was set at 0. Further details on device programming and optimization of CRT programming are reported elsewhere (15).

Follow-up and core laboratories. Baseline clinical data, electrocardiograms, echocardiograms, and bloods for assessment of renal function and amino terminal pro-brain natriuretic peptide (NT-proBNP) were collected on the day of randomization. Key information was sent to an independent randomization center prior to assigning patients to the CRT or control group. Device implantation was planned to occur within 5 days of randomization. Patients were reviewed prior to discharge, at 1 month, at 3 months, every 3 months for the first year, and then every 6 months. Detailed assessments, as at baseline, were repeated at 3 months.

Baseline and follow-up echocardiograms were sent to the core echocardiographic laboratory for analysis including LV end-systolic and -diastolic volumes, LVEF, and mitral regurgitation (16). Baseline and follow-up electrocardiograms were sent to a core therapy-delivery laboratory. Serum creatinine was measured locally. Plasma was stored at −70°C until the end of the study and then sent to the core neuroendocrine laboratory.

Predictive model. The statistical analysis plan of CARE-HF drawn up before study closure specified 15 variables that would be used as covariates in a prognostic model to predict overall patient outcome and factors that influenced the clinical effects of CRT. These included age, gender, New York Heart Association functional class, etiology of LV dysfunction, use of beta-blockers, systolic blood pressure,* QRS duration,* interventricular mechanical delay (IVMD),* severity of mitral regurgitation (MR),* left ventricular end-systolic volume index (LVESVI),* LVEF,* glomerular filtration rate,* furosemide dose >80 mg/day, NT-proBNP,* and body mass index, with allocation to the CRT or the control group as a 16th variable. For this analysis, we tested whether variables suggesting a response to CRT between baseline and 3 months (marked with *) improved the prognostic accuracy of the model compared with one using baseline characteristics only. Information on diuretic dose was not collected at 3 months. Where data were missing at 3 months, baseline data was substituted for the predicted 3-month values when measured to avoid confounding because of selective loss of information due to death or marked deterioration in patients' status. This preserved the integrity of randomization and the intention-to-treat principle while including the effects of treatment at 3 months in the model in those subjects still at risk at that time. All-cause mortality was chosen as the outcome of interest for this analysis as a robust objective marker of treatment effect. This approach tests the extent to which baseline characteristics and short-term response to CRT, presumably reflecting the amount of dyssynchrony at baseline and the extent to which it was corrected by treatment, as well as any concomitant adjustment of other therapies predicts outcome. In this model, if being assigned to CRT remains a strong predictor of a better prognosis, it implies that much of the benefit of CRT cannot be explained by dyssynchrony or its correction, at least as measured prior to or shortly after implantation.

Statistics. Baseline characteristics were described using frequency or median and interquartile range, as appropriate. Differences at baseline between randomized groups were described using the Fisher exact test or Kruskal-Wallis test for frequency counts or continuous variables. Univariate and multivariate analyses predicting all-cause mortality were developed using Cox constant proportional hazards models, including time-dependent covariates as described. Proportional hazards models were compared (baseline-only and time-dependent covariate) using Akaike information criterion, and parsimonious models were preferred unless more complex forms (e.g., those with time-dependent covariates) added to the model fit. A forward stepwise approach with entry to the model set at $p = 0.1$ and the criterion for remaining in the model set at $p = 0.05$. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

A total of 813 patients were randomly assigned to receive or not receive a CRT device, and 721 were enrolled based on a QRS duration >150 ms alone. By 3 months, 15 patients assigned to the control group and 12 patients assigned to CRT had died. Those assigned to CRT had a greater reduction in QRS, IVMD, LVESVI, MR, and NT-proBNP (logarithmic values) and a greater increase in systolic blood pressure and LVEF compared with the control group, but changes in glomerular filtration rate were similar (Tables 1 and 2).

During a median follow-up of 37.6 (range 26.1 to 52.6) months, 154 patients assigned to the control group and 101 assigned to CRT died. Univariate analysis demonstrated that most of the 15 baseline variables, with the exception of gender, QRS duration, and body mass index, predicted survival (Table 3). *Greater* IVMD at baseline predicted a *better* outcome. The relationship between prognosis and values at 3 months for ESVI, LVEF, MR, and NT-proBNP, regardless of treatment assignment, were stronger, and IVMD weaker, compared with baseline values. In the multivariable model, *baseline* variables that independently predicted shorter survival were ischemic heart disease ($p = 0.0066$) (Fig. 1), less severe IVMD ($p = 0.0029$) (Fig. 2), and more severe New York Heart Association functional

Table 1 Continuous Variables Included in Analysis, at Baseline and 3 Months

Variable	Time	Control*	CRT*	p Value for Difference Between Groups†
MR	Baseline	22.9 (10.8–34.0)	21.3 (11.6–32.9)	X
	3 months	18.8 (10.7–31.3)	14.1 (7.6–24.8)	0.0002
IVMD	Baseline	49.6 (29.6–66.1)	48.5 (31.7–67.0)	X
	3 months	51.2 (28.9–68.8)	24.8 (11.7–41.2)	<0.0001
ESVI	Baseline	121.3 (91.8–151.3)	116.8 (94.3–146.9)	X
	3 months	116.4 (85.2–149.0)	94.6 (69.9–123.5)	<0.0001
LVEF	Baseline	24.8 (21.6–29.2)	24.6 (21.4–29.0)	X
	3 months	25.1 (21.7–30.2)	29.3 (24.3–34.8)	<0.0001
Age	Baseline	66.2 (59.0–71.7)	66.5 (59.5–72.5)	X
QRS	Baseline	160 (152–180)	160 (152–180)	X
	3 months	164 (152–180)	145 (120–160)	<0.0001
NT-proBNP	Baseline	1,806 (719–3,949)	1,920 (744–4,288)	X
	3 months	1,649 (609–3,704)	1,112 (482–3,053)	0.016
Systolic BP	Baseline	110 (100–125)	110 (100–125)	X
	3 months	119 (105–130)	121 (110–140)	<0.0001
GFR	Baseline	60.9 (45.6–72.7)	59.6 (45.7–73.0)	X
	3 months	58.8 (47.1–73.7)	59.6 (45.8–77.0)	0.76
BMI	Baseline	27.0 (23.8–30.3)	26.2 (23.7–29.3)	X

*Median and interquartile range are shown. †X = no baseline differences were observed between assigned groups.
BMI = body mass index; BP = blood pressure; CRT = cardiac resynchronization therapy; ESVI = end-systolic volume index; GFR = glomerular filtration rate; IVMD = interventricular mechanical delay; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NT-proBNP = amino terminal pro-brain natriuretic peptide.

class ($p = 0.0020$) (Table 4, Fig. 3). Further independent prognostic information was provided by NT-proBNP ($p < 0.0001$) (Fig. 4) and severity of MR ($p < 0.0001$) (Fig. 5) measured at 3 months. Indeed, NT-proBNP measured at 3 months was the most powerful prognostic marker (Table 4). As models may be affected by extreme values, we repeated analyses after removing the 5% of patients with the highest and lowest levels of NT-proBNP. This did not substantially change the result, and neither did rerunning the statistical models without using the last observation carried forward approach for missing data among eligible patients at 3 months.

The unadjusted hazard ratio for mortality in patients assigned to CRT was 0.60 (95% confidence interval: 0.47 to 0.77, $p < 0.0001$). The hazard ratio after adjusting for variables measured both at baseline and at 3 months (0.67, 95% confidence interval: 0.49 to 0.91; $p = 0.0113$) was similar (Fig. 6). Removing allocation to CRT or control from the model reduced the goodness of fit.

Table 2 Categorical Variables Included in Analysis at Baseline Showing Proportions as a Percentage

Variable	Control Group	CRT
Ischemic heart disease	153 (38.0%)	186 (45.5%)
Treated with beta-blockers	288 (71.3%)	298 (72.9%)
Receiving furosemide ≥80 mg or equivalent	177 (43.8%)	175 (42.8%)
NYHA functional class IV	27 (6.7%)	23 (5.6%)
Men	293 (72.5%)	304 (74.3%)

CRT = cardiac resynchronization therapy; NYHA = New York Heart Association.

Discussion

This analysis demonstrates that MR and NT-proBNP measured 3 months after intervention were powerful independent predictors of long-term survival in the CARE-HF study. Patients assigned to CRT were more likely to have an improvement in MR and a reduction in NT-proBNP (13), which suggests that these factors may predict or mediate some of the long-term response to this therapy (5,17,18). However, the effect of CRT on long-term mortality persisted despite adjustment for these and other variables measured either at baseline or soon after intervention. Either the study failed to capture some aspects of the early benefit of CRT or the long-term clinical effects of CRT cannot be accurately predicted from either baseline measures or the short-term response. These data support the observation that patients who improve their cardiac function after receiving CRT have a better prognosis (12) but, at the same time, indicate that this is the mechanism of a relatively small proportion of the effect of CRT on long-term mortality. Accordingly, an improvement in cardiac function after implanting a CRT device is a welcome sign but an unreliable surrogate for long-term response.

One possible explanation for our findings is that cardiac dyssynchrony is a much more dynamic phenomenon than is currently appreciated. The QRS width increases during long-term follow-up (19), but the incidence of dyssynchrony, as opposed to its prevalence, has not been reported. Dyssynchrony may have been absent at baseline but developed during follow-up as part of the disease process and may have resolved in some patients

Table 3 Univariate Analysis, 1° of Freedom, Showing Relationship Between Long-Term Mortality and Variables Measured at Baseline and at 3 Months

Variable	Units	Parameter Estimate	SE	Chi-Square	p Value	Hazard Ratio	95% CI
Age	yrs	0.03336	0.00678	24.2327	<0.0001	1.034	1.020–1.048
Male	Yes	0.08430	0.14448	0.3404	0.5596	1.088	0.820–1.444
Ischemic	Yes	0.74747	0.12657	34.8759	<0.0001	2.112	1.648–2.706
NYHA functional class IV	Yes	0.87025	0.20062	18.8172	<0.0001	2.388	1.611–3.538
Furosemide ≥80 mg*	Yes	0.72052	0.12704	32.1688	<0.0001	2.055	1.602–2.637
Beta-blocker	Yes	−0.42643	0.13045	10.6860	0.0011	0.653	0.506–0.843
BMI	kg/m^2	−0.01381	0.01339	1.0640	0.3023	0.986	0.961–1.013
Systolic BP	mm Hg	−0.01578	0.00388	16.5315	<0.0001	0.984	0.977–0.992
Systolic BP†	*mm Hg*	*−0.01628*	*0.00360*	*20.4542*	*<0.0001*	*0.984*	*0.977–0.991*
MR	U‡	0.02075	0.00438	22.4824	<0.0001	1.021	1.012–1.030
MR†	*U*‡	*0.02282*	*0.00344*	*44.0400*	*<0.0001*	*1.023*	*1.016–1.030*
ESVI	ml/m^2	0.00251	0.00124	4.1181	0.0424	1.003	1.000–1.005
ESVI†	*ml/m^2*	*0.00446*	*0.00113*	*15.6954*	*<0.0001*	*1.004*	*1.002–1.007*
LVEF	%	−0.03547	0.01181	9.0175	0.0027	0.965	0.943–0.988
LVEF†	%	*−0.04676*	*0.01022*	*20.9506*	*<0.0001*	*0.954*	*0.935–0.974*
NT-proBNP	pg/ml§	0.49937	0.05691	77.0084	<0.0001	1.648	1.474–1.842
NT-proBNP†	*pg/ml*§	*0.54872*	*0.05356*	*104.9740*	*<0.0001*	*1.731*	*1.559–1.923*
GFR	$ml/min/m^2$	−0.01687	0.00367	21.1283	<0.0001	0.983	0.976–0.990
GFR†	*$ml/min/m^2$*	*−0.01642*	*0.00346*	*22.5253*	*<.0001*	*0.984*	*0.977–0.990*
QRS	ms	0.0001411	0.00331	0.0018	0.9660	1.000	0.994–1.007
QRS†	*ms*	*0.00413*	*0.00269*	*2.3483*	*0.1254*	*1.004*	*0.999–1.009*
IVMD	ms	−0.01262	0.00231	29.8065	<.0001	0.987	0.983–0.992
IVMD†	*ms*	*−0.00841*	*0.00239*	*12.3315*	*0.0004*	*0.992*	*0.987–0.996*
CRT	Yes	−0.50739	0.12810	15.6881	<.0001	0.602	0.468–0.774

Values that were remeasured are in *italics*. *Furosemide 80 mg/day was pre-specified in the analysis plan as indicating high-dose diuretic. †Time-dependent covariate model, with 3-month value when available and baseline value if not. This preserves the integrity of randomization. ‡Calculated as the area of the color-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimeters. §Logarithmic values used in analysis for brain natriuretic peptide.

CI = confidence interval; QRS = width of QRS complex on the surface electrocardiogram; other abbreviations as in Tables 1 and 2.

who had it at baseline. Dyssynchrony may be absent at rest but present during exercise or cardiac stress (20,21). As there is great uncertainty about how, under what physiological conditions, and how often dyssynchrony should be measured, the concept of measuring dyssynchrony to predict the response to CRT may be either too complex for widespread clinical use or futile.

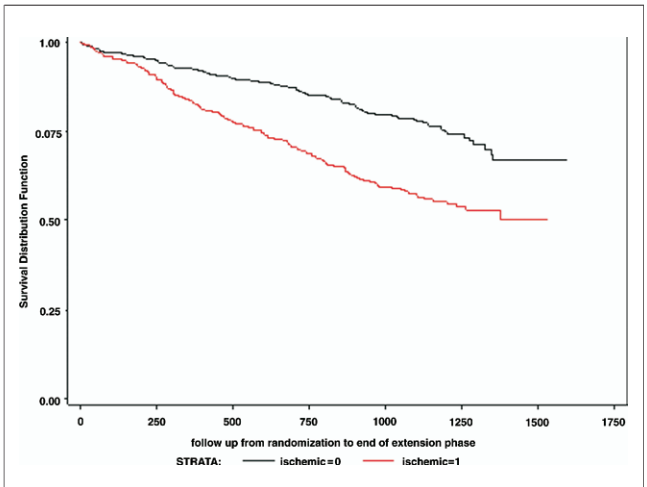

Figure 1 Outcome in Patients With and Without Ischemic Heart Disease as the Reported Cause of LVSD

Hazard ratio for patients with ischemic heart disease compared with those without ischemic heart disease was 1.546 (95% confidence interval 1.129 to 2.118; p = 0.0066). LVSD = left ventricular systolic dysfunction.

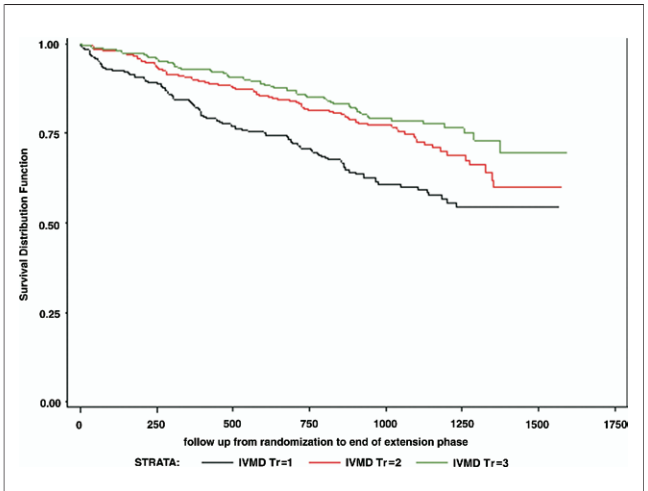

Figure 2 Outcome in Patients According to Baseline Duration of IVMD

Values for interventricular mechanical delay (IVMD) of 38 and 61 ms defined the upper and lower boundaries of the middle tercile. The hazard ratio for those in the highest versus lowest tercile was 0.473 (95% confidence interval: 0.340 to 0.657; p < 0.0001). Tr = tercile.

Table 4 Multivariable Analysis, in Order of Strength of Relationship, Showing Those Variables That Made an Independent Contribution to the Model That Best Predicted All-Cause Mortality

Variable	Units	Parameter Estimate	Standard Error	Chi-Square	p Value > Chi-Square	Hazard Ratio	95% CI
BNP*	pg/ml†	0.47914	0.06890	48.3659	<0.0001	1.615	1.411–1.848
MR*	U‡	0.01877	0.00443	17.9233	<0.0001	1.019	1.010–1.028
Ischemic	Yes	0.43579	0.16049	7.3729	0.0066	1.546	1.129–2.118
IVMD	ms	−0.00859	0.00289	8.8489	0.0029	0.991	0.986–0.997
NYHA functional class IV	Yes	0.80120	0.25893	9.5747	0.0020	2.228	1.341–3.701
CRT	Yes	−0.39783	0.15700	6.4210	0.0113	0.672	0.494–0.914

*Time-dependent covariate model, with 3-month value taken when available and baseline value if not. This preserves the integrity of randomization. †Logarithmic values used in analysis for BNP. ‡Calculated as the area of the color-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimeters.
BNP = brain natriuretic peptide; other abbreviations as in Tables 1 to 3.

Among markers of ventricular dysfunction, only NT-proBNP retained independent prognostic value, perhaps because it is a more comprehensive single measure of cardiac function or because it also reflects renal function, another powerful prognostic factor in patients with heart failure (22). Indeed, in the CARE-HF trial, the main determinants of NT-proBNP were age, glomerular filtration rate, LVEF, MR, and, at 3 months, randomization to CRT (23). Despite the relationship between MR and NT-proBNP, each retained independent prognostic value in the multivariable model, suggesting that the circulatory stress due to MR is not wholly reflected by plasma concentrations of NT-proBNP. On univariate analysis, LVEF and ESVI measured at baseline predicted mortality but values measured at 3 months were much stronger, implying that improvement in echocardiographic ventricular function, which is more likely to occur in patients receiving effective CRT, indicates that a patient is likely to have a better outcome. However, improved echocardiographic ventricular function was not an independent predictor of outcome. This is a complex problem. Disease etiology is an important determinant of the improvement in ventricular function with CRT and also of the severity of IVMD but not of the effects of CRT on survival (2,24).

The QRS duration has been used as a marker of ventricular dyssynchrony and has predicted a worse prognosis in epidemiological studies and clinical trials of heart failure (19,25). This has been interpreted as evidence that cardiac dyssynchrony predicts an adverse outcome in patients with heart failure, but this has not yet been substantiated by imaging studies. The QRS duration is also a marker of the severity of ventricular dysfunction (26). The inability of QRS duration to predict mortality in this study could reflect the inclusion only of patients who had a prolonged QRS.

Patients with a longer interventricular mechanical delay measured by echocardiography had a better prognosis. This may reflect a poor prognosis among patients with severe right ventricular dysfunction that led to a similar delay in the time to pulmonary and aortic ejection. On the other hand, greater delay in aortic compared with pulmonary ejection, reflecting greater left intraventricular dyssynchrony and inefficiency, might be associated with a better prognosis

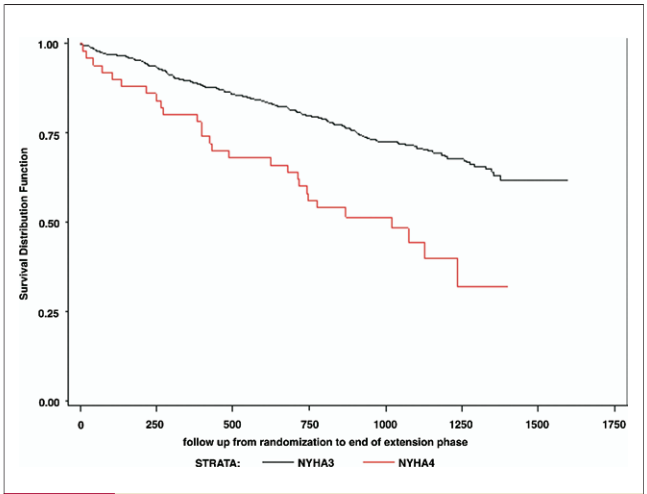

Figure 3 Outcome in Patients According to Baseline NYHA Functional Class

Hazard ratio for those in New York Heart Association (NYHA) functional class IV versus III was 2.228 (95% confidence interval: 1.341 to 3.701; p = 0.0020).

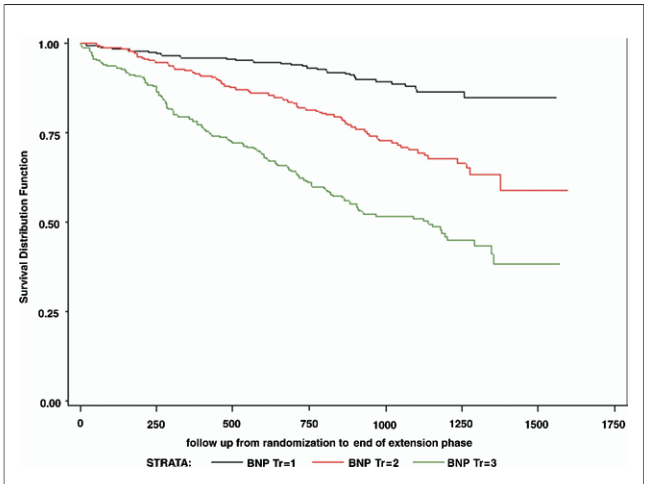

Figure 4 Outcome in Patients According to Plasma Concentration of NT-proBNP Achieved by 3 Months

Plasma concentrations of amino terminal pro–brain natriuretic peptide (NT-proBNP) of 812 (log: 6.7) and 2,622 (log: 7.8) pg/ml defined the upper and lower boundaries of the middle tercile. The hazard ratio for those in the highest versus lowest tercile was 5.682 (95% confidence interval: 3.819 to 8.455; p < 0.0001). Tr = tercile. BNP = brain natriuretic peptide.

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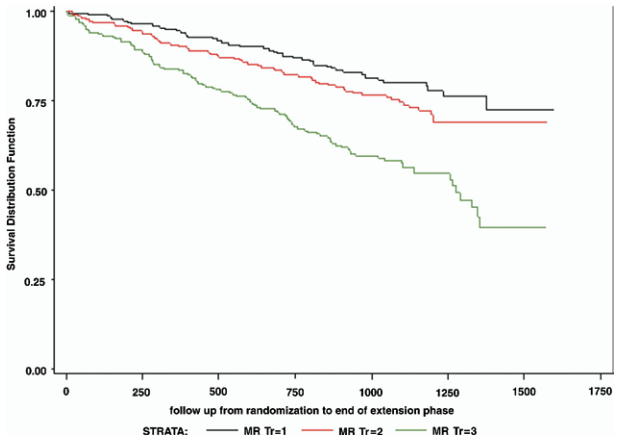

Figure 5 **Outcome in Patients According to Severity of MR Index at 3 Months**

Values for mitral regurgitation (MR) index of 11.1 and 24.2 units defined the upper and lower boundaries of the middle tercile. The hazard ratio for those in the highest versus lowest tercile was 2.673 (95% confidence interval: 1.881 to 3.799; $p < 0.0001$). Tr = tercile.

for several reasons. In a synchronous ventricle, global LVEF will represent the sum of segmental myocardial contraction, but in a dyssynchronous ventricle, global ejection fraction will be an underestimate of total contractile function. The reason for the abrupt early increase in LVEF with CRT is presumably due to correction of dyssynchrony, which reveals the patient's true underlying global contractile function. Dyssynchrony also reflects dysfunctional but viable myocardium, which may be more likely to respond to treatment such as beta-blockers (27) and CRT (28). The widely held view that patients with extensive dyssynchrony have an intrinsically worse prognosis needs to be examined in other datasets. A previous analysis of the CARE-HF trial showed that patients with more marked IVMD had a slightly greater response to CRT, in terms of death or hospitalization for a major cardiovascular event, but that patients with less marked IVMD still benefited (29). Other randomized controlled trials have either failed to show that baseline measures of ventricular dyssynchrony predict benefit with CRT or showed results similar to ours (9,30). It is possible that more advanced imaging techniques, including tissue Doppler imaging (5,17) and cardiac magnetic resonance imaging (11), will be able to predict the response of patients to CRT, but analysis of data from the CARE-HF trial suggests that observational studies should generally be interpreted with caution. Dyssynchrony and CRT may both be associated with a better outcome and therefore observational trials may be unable to distinguish between the effects of disease and of treatment. Recently, the PROSPECT study failed to predict improvement in clinical status or LV function, even when sophisticated echocardiographic techniques, including tissue Doppler imaging, were used (10). It is also possible that the relationships among outcome, the highly variable patients, and myocardial substrate and the varied response to CRT of cardiac function, dyssynchrony, MR, and neuroendocrine activation are too complex to be explained by our statistical model, which may not have included important unmeasured variables. However, if this is the case, it is also unlikely that any simple clinical measure will be adequate to predict response.

Among patients assigned to a CRT device in the CARE-HF trial, those who had persistent moderate or severe MR and/or persistently elevated NT-proBNP at 3 months did less well than other patients and might be considered for additional interventions. A review of the programming of the timing of atrioventricular or interventricular stimulation is the quickest, simplest, and least expensive first option (31). A review of pharmacological therapy may identify suboptimal use of diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, and/or angiotensin receptor blockers or that agents such as nonsteroidal anti-inflammatory drugs have not been withdrawn. For patients who remain severely symptomatic despite such measures, palliative care or advanced interventions such as an LV assist device or heart transplantation might be considered. Whether mitral valve surgery should be considered in patients with persistent moderate-to-severe MR is controversial (32).

The CARE-HF trial enrolled only 92 patients (11%) based on a QRS width of 120 to 149 ms, and these patients had to have 2 or more echocardiographic measures of dyssynchrony. Applying the overall analysis to this subgroup should be done with caution because of the additional dyssynchrony inclusion criteria and because there were few patients or events in this subgroup. This analysis cannot draw any conclusions about the effects of CRT in patients with QRS <150 ms who did not have markers of dyssynchrony.

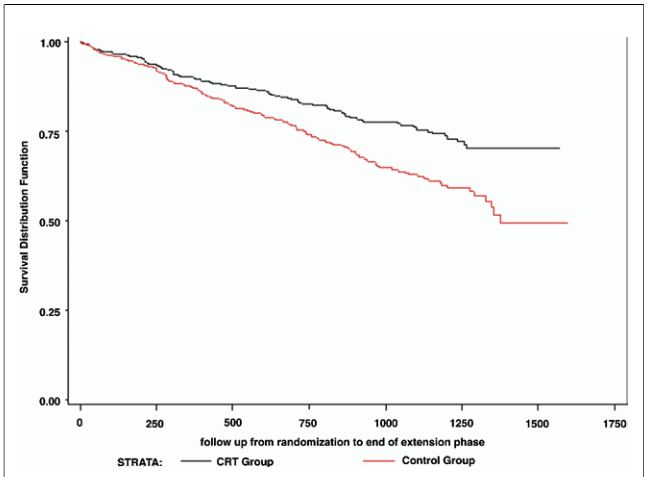

Figure 6 **Mortality According to Assigned Therapy, Adjusting for Baseline Variables and Initial Response**

The adjusted hazard ratio for those assigned to cardiac resynchronization therapy (CRT) was 0.672 (95% confidence interval: 0.494 to 0.914; $p = 0.0113$). The unadjusted hazard ratio was 0.60 (95% confidence interval: 0.47 to 0.77; $p < 0.0001$). The curves do not differ appreciably from those derived from unadjusted data and published previously in Cleland et al. (2,3).

Conclusions

A combination of baseline variables and measures of the early response to therapy predicted the overall long-term mortality of patients enrolled in the CARE-HF trial, regardless of assigned treatment. However, the reduction in long-term mortality by CRT was poorly explained by baseline measures of cardiac dyssynchrony or the short-term response to biventricular pacing. These data suggest that patients should be selected for atriobiventricular pacing using the entry criteria of successful randomized controlled trials. It is not clear that identification of dyssynchrony on a resting echocardiogram is an appropriate way to choose patients for CRT, especially if their QRS is >150 ms.

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Key Words: heart failure ■ cardiac resynchronization therapy ■ randomized controlled trial.